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Photoacoustic-Ultrasound Tomography: A New Window into Developmental Toxicity

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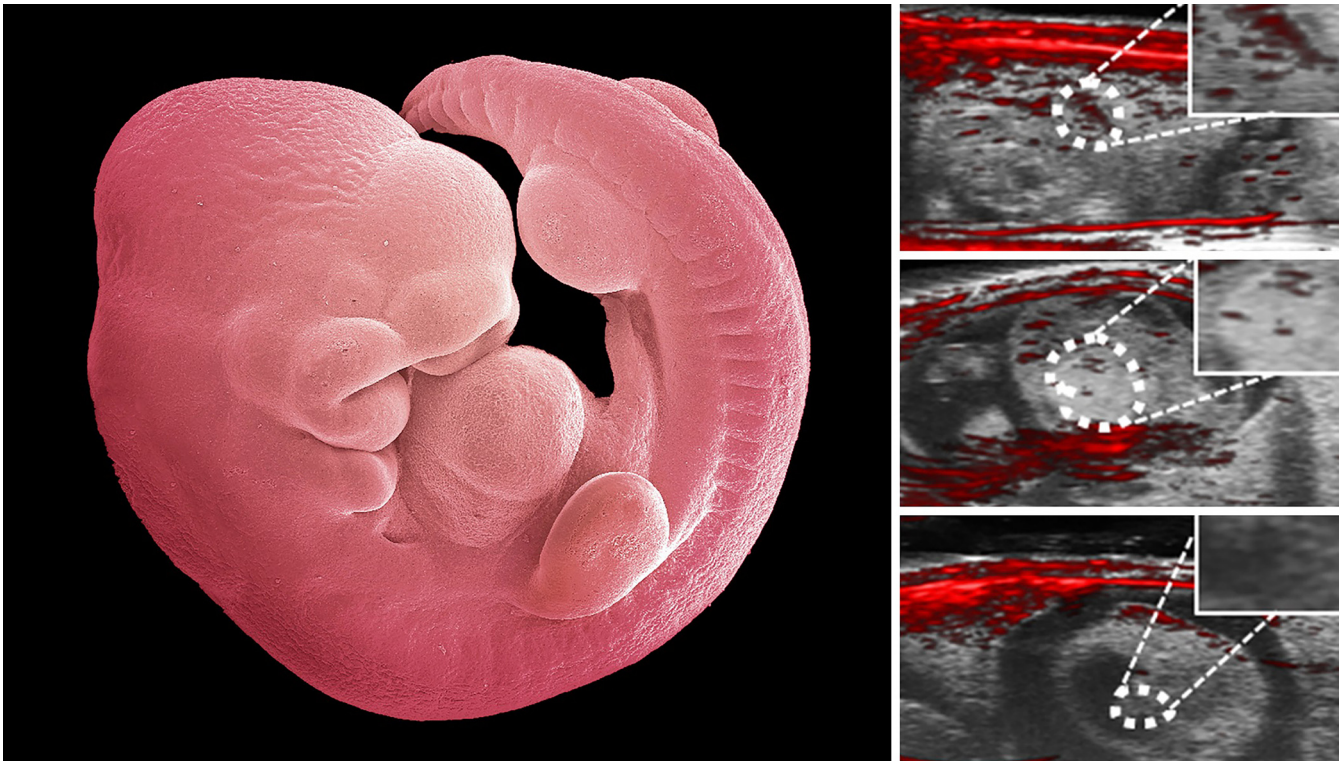
Worldwide, birth defects affect 3%–6% of infants and account for 20% of all infant deaths.[1] With mounting evidence for links between environmental exposures and birth outcomes,[2,3] there is an need for accurate screening strategies for timely diagnosis and treatment of fetal abnormalities. According to the authors of a recent study published in *Environmental Health Perspectives*, early detection of developmental defects in mice was achieved using a novel dual-modality imaging technique that can overcome some of the challenges of traditional ultrasound technology.[4]

Birth defects arise from unknown causes in roughly half of all cases.[5,6] Congenital heart defects are the most common type of birth defect[7] and are among the top eight causes of infant mortality.[8] Mixed evidence associates congenital heart defects with prenatal proximity to landfills and exposures to air pollution, metals, pesticides, solvents, disinfection by-products, and high ambient temperatures.[9,10,11]

Ultrasound imaging techniques can detect some developmental defects before birth, but despite significant advances, their use is limited to later stages of development. However, even in the second trimester more than 50% of congenital heart abnormalities are not detected by routine fetal ultrasound.[12] In addition, conventional ultrasound cannot measure functional parameters such as tissue oxygen saturation (SaO_2) and hemoglobin content (HbT). These two early indicators of alterations in embryo circulation typically precede gross morphological changes.[13,14]

A newer tool, photoacoustic-ultrasound (PA-US) tomography, combines the specificity, high contrast, and deep-tissue penetration of optical and acoustic imaging technologies to provide details about organ structure and function.[15] In this hybrid technology, optical energy is delivered into biological tissues, resulting in ultrasonic emissions that can be analyzed to produce images.[16] Because optical absorption is directly related to physiological properties such as SaO_2 and HbT content, different tissues will produce different photoacoustic signals, which can be translated into extremely detailed three-dimensional pictures of the target area.[17] Although PA-US tomography is a promising clinical tool broadly applied in disease monitoring, functional imaging, and therapy and surgery guidance,[18] this is the first time it was tested for assessing developmental toxicity.

In the study, investigators used dual-modality PA-US imaging to examine early embryo morphology and markers of embryonic tissue oxygenation and function in mice, after exposure to methylmercury chloride (MMC), a potential neuro- and cardiotoxicant. Pregnant dams received either a high MMC dose, low MMC dose, or saline control for 6 consecutive days. Exposure occurred during a period equivalent to weeks 2–4 of human gestation, when early organogenesis begins and the risk of developmental



Left: The heart bulge of this 12-day-old mouse embryo is visible in the center of its body. Scanning electron micrograph, magnification 20× when printed at 10 cm wide. Right: A new tomographic technique enabled investigators to pinpoint when heart abnormalities started in embryos that received low (middle) and high (bottom) doses of MMC (the top panel shows the control). Images, left to right: © Steve Gschmeissner/Science Photo Library; Qiu et al.[4]

abnormalities and miscarriage is highest.[19,20] Embryos from treated and control dams were evaluated for pathological changes using PA-US imaging. That technique enabled detection of differences between the high-dose and control groups in overall embryo size and cardiovascular function, results that were confirmed by *ex vivo* histopathological analyses. In the low-dose group, quantification of SaO_2 and HbT values allowed detection of functional abnormalities that preceded apparent morphological changes and would have eluded diagnosis by conventional ultrasound alone.

Fuller Bazer, chair of the Physiology of Reproduction Program at Texas A&M University, notes that the dosages used in the study were high relative to concentrations that are toxic to humans. However, the authors' main focus was testing the technology's performance. Given the results, says Bazer, who was not involved in the study, PA-US imaging shows promise as a noninvasive means of detecting developmental abnormalities. With further refinement, he suggests, PA-US imaging could prove instrumental in identifying unique developmental changes during normal gestation, or in mouse models of disease with detrimental effects on fetal and placental development.

"Our study provides a new high-resolution, real-time imaging method for *in vivo* evaluation of embryonic development," says Qingliang Zhao, senior author of the study. "We believe that dual-modality PA-US imaging has great potential in developmental biology research." The technology is not yet ready for use in humans, Zhao says. However, he asserts that the application of photoacoustic contrast agents and the optimization of detector bandwidth—both of which are the subject of published studies[21,22]—would drastically improve the resolution and imaging depth of the PA-US system. Such an approach could prove useful in preclinical studies and clinical applications.

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